Treatment and prognosis of COVID-19: Current scenario and prospects (Review)

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Abstract. SARS-CoV-2 is the seventh member of the family of coronaviruses that can cause infections in humans, termed as COVID-19, which is now a global pandemic. Because it is a novel virus, considerable efforts and extensive studies are needed to fully understand its characteristics. Its symptoms and severity range from mild to critical, depending on several factors, such as host susceptibility to the virus and their immune system, with the most common symptoms being fever, fatigue, sore throat and runny nose. There is no clear treatment available yet, though several options are being explored, with research for vaccines being at the forefront. Traditional Chinese Medicine may also be used as a treatment option. Since this virus is similar to the SARS-CoV and MERS viruses, considerable insight can be gained from previous studies. Although many patients recover completely, there are several factors that lead to poor prognosis. This review summarizes the research carried out so far in terms of treatment options and prognosis factors associated with COVID-19.

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Abbreviations: ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; ACE2, angiotensin-converting enzyme 2; G-SCF, granulocyte colony-stimulating factor; IP10, interferon induced protein-10; MCP-1, monocyte chemoattractant protein-1; MIP1A, macrophage inflammatory protein 1α; TNFα, tumor necrosis factor α; ICU, intensive care unit; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; IFNγ, interferon γ; PDGF, platelet derived growth factor; VEGF, vascular endothelial growth factor; CT, computed tomography; RT-PCR, reverse transcriptase polymerase chain reaction; RdRp, RNA-dependent RNA polymerase; ECMO, extracorporeal membrane oxygenation; MAs, monoclonal antibodies; IgG, immunoglobulin G; IgM, immunoglobulin M; RAS, renin-angiotensin system; Akt, protein kinase B; CRRT, continuous renal replacement therapy; IVIg, intravenous immunoglobulin; LNP, lipid nanoparticles; RBD, receptor binding domain; VLP, virus-like particles; ERK/MAPK, extracellular regulated protein kinases/mitogen activated protein kinase; PI3K/AKT/mTOR, phosphatidylinositol 3 kinase/protein kinase B/mammalian target of rapamycin; AT1R, angiotensin II type 1 receptor; TCM, Traditional Chinese Medicine; PLR, platelet-to-lymphocyte ratio; LMWH, low molecular weight heparin; DIC, disseminated intravascular coagulation

Key words: SARS-CoV-2, COVID-19, coronavirus, treatment, prognosis, features

Contents

1. Introduction

Viruses of the *coronaviridae* family are RNA viruses with enveloped genomes of linear single-stranded plus strands and are widely distributed in nature (1). Previously, six types of coronavirus that could infect humans were identified, namely, HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV and MERS-CoV (2). A novel type of coronavirus was accidentally discovered in Wuhan in December 2019, which is now known as SARS-CoV-2. These viruses can cause gastrointestinal, respiratory, and neurological symptoms (2).

The understanding of the physical and chemical characteristics of SARS-CoV-2 is derived mainly from studies on SARS-CoV and MERS-CoV. SARS-CoV-2 is sensitive to ultraviolet radiation and heat treatment (30 min at 56˚C) (3). Chemicals such as ether, 75% ethanol, chlorine-containing disinfectants, peracetic acid and chloroform can effectively inactivate the virus; however, chlorhexidine cannot (4).

The sequence of SARS-CoV-2 is 96% identical to that of the coronavirus that infects bats (5). Therefore, it is assumed

that bats are the main source of the virus. Current evidence collectively shows that the virus was transmitted to humans through wildlife that was illegally sold in the South China seafood wholesale market (6).

By comparing the seven conserved non-structural proteins, Zhou *et al* (7) found that SARS-CoV-2 belongs to the SARS-CoV family. In addition, the receptor that mediates its entry into cells, such as angiotensin-converting enzyme 2 (ACE2), is similar to that of SARS-CoV (7).

Since December 2019, an epidemic of the disease caused by SARS-CoV-2 infection, named COVID-19 (8), broke out in China, and is now a global pandemic, with high mortality rates. In view of the rapid transmission and a lack of effective therapies or vaccines, research into the preventive measures or treatment of the disease is urgently needed. This review is a collection of current studies and ongoing research on the treatment strategies and prognosis of COVID-19.

2. Clinical features of COVID-19

Clinical presentation. Based on the current epidemiological survey (9), the incubation period for SARS-CoV-2 is 1-14 days. Fever, fatigue and dry cough are the main symptoms. A few patients present with nasal obstruction, runny nose, sore throat and diarrhea. In severe cases, dyspnea and/or hypoxemia usually occur one week after disease onset (10), and rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, bleeding, and coagulation dysfunction, that are difficult to cure. It is worth noting that the pyrogenic response of patients with severe and critical disease can be moderate to low, or the patients might have no obvious symptoms (11). Patients with mild disease only present with low fever and slight asthenia, without pneumonia. Currently, the prognosis of most patients is good, with only a few patients being reported as critically ill and the mortality rate ranging from 0 to 14.6% (12,13). However, the prognosis of the elderly and those with underlying chronic diseases is poor, and the symptoms of children are relatively mild (14,15).

Laboratory tests and imaging results. Laboratory analysis of blood samples of positive cases revealed either a lower or a normal white blood cell count and a lower lymphocyte count. Some patients showed increased levels of liver enzymes, lactate dehydrogenase, muscle enzymes and myoglobin (6). Some critical patients presented with increased troponin levels; however, most patients showed increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) with normal procalcitonin levels. In severe cases, D-dimer levels increased and peripheral blood lymphocyte count decreased progressively (16,17). The nucleic acids of SARS-CoV-2 can be detected in nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, stool, and other specimens (18). Patients with severe and critical conditions often have elevated inflammatory factors. It has also been reported that the plasma levels of interluekin-2 (IL-2), IL-7, IL-10, granulocyte colony-stimulating factor (G-SCF), interferon induced protein-10 (IP10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1α (MIP1A), and tumor necrosis factor α (TNFα) levels in ICU (Intensive Care Unit) patients were higher than those of non-ICU patients, and initial plasma levels of IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, basic fibroblast growth factor (FGF), G-CSF, granulocyte-macrophage colony stimulating factor (GM-CSF), interferon γ (IFNγ), IP10, MCP1, MIP1A, MIP1B, platelet derived growth factor (PDGF), TNFα, and vascular endothelial growth factor (VEGF) were higher in both ICU patients and non-ICU patients, when compared to that in healthy individuals (19-21).

Chest Computed Tomography (CT) imaging showed multiple small patches and interstitial changes in the outer zone of the lung during the early course of the disease (22). An increase in ground-glass and infiltrating shadows were seen in both lungs in the middle and late stages of the disease. In severe cases, consolidation of lung may occur, but pleural effusion is rare (15,23). However, normal CT findings by themselves cannot rule out a SARS-CoV-2 infection. Though the reverse transcriptase polymerase chain reaction (RT-PCR) test has been used as a reference standard to diagnose COVID-19, an RT-PCR confirmed positive case may have normal CT findings. Hence, chest CT findings were removed from the diagnostic criteria. Therefore, the exact diagnosis of COVID-19 should be based on RT-PCR and gene sequencing (24). However, the genetic diversity and rapid evolution of SARS-CoV-2 may result in false-negative or false-positive results. Hence, in order to make a better diagnosis, the RT-PCR results must be combined with other detection results and clinical characteristics (25). Chan *et al* (26) compared three RT-PCR assays and found that an assay targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel) showed high sensitivity and specificity.

Serological changes also have important significance in the diagnosis of COVID-19. Detection of IgM and IgG antibodies may predict the burden of the viral infection. However, since IgM responses are not specific, and the development of IgG occurs over a few weeks, serological assays may be not applicable for acute infections, but for advanced cases (27). Additionally, Zhang *et al* (28) reported that the seropositive rate increases with the duration of the disease in symptomatic cases and seroconversion occurs early in severe cases, while specific antibody responses are generated at later stages in asymptomatic cases. Hence, serological characteristics can be used to distinguish the severity of the disease. Besides, the symptomatic cases have heavy viral burden than asymptomatic cases. Because a large number of viruses entering the body will inevitably cause damage to the body, and the body will show the corresponding symptoms. Furthermore, asymptomatic patients exhibit later plasma antibody generation and lower antibody titer than symptomatic patients. It is probably because that the body immune response intensity is partially dependent on the number of virus. These clinical features can be seen in Table I.

3. Current COVID-19 treatment options

For the management of COVID-19, there is a need to strengthen supportive care and closely monitor the vital signs, laboratory examination results and imaging findings of the patients. Providing effective oxygen therapy on time is also essential. Antiviral treatment in the form of α-interferon aerosol inhalation, lopinavir/ritonavir, remdesivir, favipiravir, betulinic acid, oseltamivir (29), ribavirin (combined with interferon or

Table I. Clinical features of COVID-19.

Groups	Clinical features
Asymptomatic	Later seroconversion (24)
Mild	Low fever, fatigue, dry cough, slight asthenia (9), increased CRP and ESR (13,14)
Moderate	Increased CRP and ESR, (13,14) increased ground-glass and infiltrating shadows in both lungs (20,21).
Severe and critical	Dyspnea, hypoxemia, (9) ARDS, septic shock, metabolic acidosis, bleeding, coagulation dysfunction, increased troponin, increased CRP and ESR, increased D-dimer, decreased peripheral blood lymphocyte count, (13,14) elevated inflammatory factors, (16) increased ground-glass and infiltrating shadows in both lungs, consolidation of lung, (20,21) earlier seroconversion, high viral burden (24,25).

ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

lopinavir/ritonavir), resochin and arbidol hydrochloride can be used; however, the right dosage and treatment course needs to be followed for these drugs. A recent study suggests that chloroquine and hydroxychloroquine do not work well in clinical application (30). Furthermore, adverse reactions of the above drugs, contraindications, and interactions with other drugs should be closely monitored. Uninformed or inappropriate use of antibiotics, especially a combined use of broad-spectrum antibiotics, should be avoided (29,31).

For severe cases or critically ill patients, on the basis of symptomatic treatment, secondary infections and complications should be actively prevented or treated, any underlying diseases treated, and timely organ function support should be provided (15). For the treatment of pregnant women, the number of gestational weeks should be considered, drugs that have as less an impact on the fetus as possible should be chosen, and knowledge on whether to treat the patient after the termination of pregnancy is required (15).

Further, as this disease belongs to the category of Traditional Chinese Medicine (15), different regions may continue to provide dialectical treatment according to the severity of illness and local climate (32), and the specific characteristics of patients (15).

Numerous studies and clinical trials are underway to develop effective treatment options for COVID-19. Corticosteroids can suppress lung inflammation, hence they have been used to treat SARS and MERS. However, they may also inhibit the immune response of the patient, thereby slowing the elimination of pathogens. In addition, available observational data indicate that corticosteroids can increase mortality and secondary infection rates when treating infections caused by influenza, SARS and MERS viruses (33). Therefore, corticosteroids should be used with caution. The World Health Organization (WHO) guidelines for clinical care released on January 28, clearly state that routine use of systemic corticosteroids to treat viral pneumonia or acute respiratory distress syndrome is not recommended, unless supported by a specific reason (34). The treatment methods and relevant drugs or agents are listed in Table II.

Oxygen therapy. Administration of timely and effective oxygen therapy to patients with COVID-19 is recommended. If possible, the patients should be treated with mixed inhalation of hydrogen and oxygen (H_2/O_2: 66.6/33.3%) (15). Patients with severe cases of COVID-19 rapidly progressed to ARDS, causing multiple organ failures and even death (35). Therefore, respiratory symptoms need to be treated urgently. For example, Zhan *et al* (36) reported that extracorporeal membrane oxygenation (ECMO) technology was successfully used to treat a patient with COVID-19. This suggests that early application of ECMO can effectively reduce the deterioration and enhance recovery of the disease.

Another study reported that the drugs acetazolamide, nifedipine and phosphodiesterase inhibitors can also be used to adjunctively treat COVID-19, thus improving lung ventilation conditions (37).

Immunotherapy. Zhou *et al* (7) reported a clear trend of IgG and IgM titer increase by monitoring the serum viral antibody levels in infected patients. The IgG-positive samples could neutralize the virus to some extent. According to research by experts, most patients with new coronavirus infections will consistently produce new coronavirus-specific antibodies after treatment and rehabilitation, and these specific antibodies can effectively kill and eliminate the virus. On February 8, 2020, the plasma antibodies from convalescent patients were used to treat patients for the first time at the First People's Hospital of Jiangxia District/Concord Jiangnan Hospital. Nine critically ill patients in this hospital received the treatment, and three serum samples were provided to critically ill patients in other hospitals. Based on the condition of severely ill patients in this hospital, after 12 to 24 h of treatment, blood oxygen saturation and the proportion of lymphocytes increased and the main inflammatory indicators decreased significantly. The clinical signs and symptoms began to improve comprehensively. Administering this special plasma product is the most effective method to treat a new coronavirus infection at present and can significantly reduce the mortality of critically ill patients (38). An envelope-anchored spike protein (S protein) mediates coronavirus entry into host cells by first binding to a host receptor and then fusing viral and host membranes (39). During entry, the virus binds to a receptor on the surface of host cells (40). The receptor is known as ACE2 (41,42). In addition, work carried out by Yi and his team at Wuhan Institute of Viruses (43), Chinese Academy of Sciences, shows that SARS-CoV-2, similar to SARS-CoV, enters cells through ACE2, suggesting that drugs targeting ACE2 and SARS drugs may be used to treat COVID-19, which is worthy of further

Table II. Treatment methods for COVID-19 based on different mechanisms.

Mechanisms or methods	Drugs or agents
Oxygen therapy	Mixed inhalation of hydrogen and oxygen (H_2/O_2:66.6%/33.3%), (31) extracorporeal membrane oxygenation technology (15).
Immunotherapy	Convalescent patient plasma, (15) monoclonal antibodies, (45) interferon, immunomodulatory agents (baricitinib, imatinib, dasatinib, and cyclosporine) (41)
Virus blocking and pathway inhibitors	Resorcinolnaphthalein, 1-[(2-dimethylamino)ethylamino]-4-(hydro xymethyl)-7-[(4-methylphenyl)sulfonyloxy]-9H-xanthene-9-one, (47) ACE inhibitors, AT1R inhibitors, (48) APN01, camostat, nafamostat, bromhexine, aprotinin, chlorpromazine, baricitinib, ruxolitinib (7), MK-2206, niclosamide, diltiazem, nitazoxanide, tizoxanide, valinomycin, the inhibitor of ERK/MAPK and PI3K/AKT/mTOR signaling pathways (sirolimus, everolimus, metformin) (7).
Suppression of cytokine storms and bacterial infections	Artificial liver blood purification techniques(CRRT, blood/plasma perfusion, absorption, plasma replacement), (47,49) non-steroidal anti-inflammatory medication, immunosuppressants, IFN-λ, corticosteroids, the cytokine antagonists, blockers and inhibitors, intravenous immunoglobulin, mesenchymal stem cells, sphingosine-1-phosphate receptor 1 agonist, increased vascular permeability, (52-54) tocilizumab, sarilumab, microecological regulators combined with Traditional Chinese Medicine (55)
Nucleoside analogues and protease inhibitors	Favipiravir, ribavirin, remdesivir and galidesivir, disulfiram, lopinavir, ritonavir, (55,56) inhibitors towards SARS-CoV-2 M^{pro}[(S)-N-Benzyl-3-((S)-2-cinnamamido-3-cyclohexylpropanamido)-2-oxo-4-((S)-2-oxopyrrolidin-3-yl) butanamide (referred to as 11r), pyridone-containing α-ketoamide derivative of 11r (referred to as 13b), nelfinavir] (7)
Anticoagulant therapy	IVIg, low molecular weight heparin, plasma exchange (44,50)
Vaccine research	RNA vaccines (LNP-encapsulated mRNA, LNP-encapsulated mRNA encoding RBD, LNP encapsulated mRNA cocktail encoding VLP), DNA vaccines (ChAdOx1 nCoV-19, INO-4800), vaccines based on protein subunit, viral vector virus-like particles, inactivated virus, live attenuated virus (59-61)

CRRT, continuous renal replacement therapy; IVIg, intravenous immunoglobulin; LNP, lipid nanoparticles; RBD, receptor binding domain; VLP, virus-like particles; ERK/MAPK, extracellular regulated protein kinases/mitogen activated protein kinase; PI3K/AKT/mTOR, phosphatidylinositol 3 kinase/protein kinase B/mammalian target of rapamycin; AT1R, angiotensin II type1receptor.

research. A number of related drugs are also being tested in clinical trials (7).

The RNA of the SARS-CoV-2 sits at the core, surrounded by nucleocapsid proteins, which are coated with spike proteins, envelope proteins and membrane proteins. In addition to these proteins that maintain the structure of the virus, viral RNA can also direct the production of other viral proteins (present in infected cells and not in viral particles) that are not involved in the structure of the virus. These proteins are foreign to the host, and the body produces antibodies against them. As a result, though individuals infected with SARS-CoV-2 can produce a wide variety of antibodies against the virus, only antibodies that recognize the proteins on the surface of the virus particles might have an antiviral effect. Antibodies against S protein, known as neutralizing antibodies, bind to S protein and block its binding to ACE2, thus protecting host cells. In addition, non-neutralizing antibodies bind to the virus through its variable region, while the constant region binds to the phagocytes, thus greatly facilitating phagocytes to clear the virus. However, this pattern can lead to the overactivation of non-specific immune cells, releasing large amounts of pro-inflammatory factors, typically IL-1, IL-6 and tumor necrosis factor (TNF), forming so-called cytokine storms, which are an important cause of ARDS and multiple organ dysfunction syndrome (44). Moreover, neutralizing antibodies are powerless against viruses that have already entered the host cells. They can only prevent most of the virus from entering the host cells; however, a small part of the virus can still enter the host cells. For viruses that enter the cells, their death depends on T cells in the body. Viruses that invade cells express information about their encoded proteins on the surface of the infected cell, and T cells recognize this information to attack the infected cell and ultimately kill both the infected cells and the viruses inside.

In addition, since the plasma of the donor is an alien component to the patients, it is likely to cause an allergic reaction or infection caused by blood transfusion, such as acquired immune deficiency syndrome (AIDS) and syphilis. Therefore, plasma therapy is risky and suitable for critically ill patients with low immunity and without a cytokine storm, and is not recommended for patients with mild cases. In conclusion, plasma therapy must be used with caution, and should be further studied.

Monoclonal antibodies (MAs) are generally regarded as effective and therapeutically specific towards viral infections because they prevent the virus from entering the host

cells through binding with the S protein or ACE2 receptor. While MAs are highly effective, their rapid mass production is unrealistic and therefore unlikely to be appropriate for this burgeoning pandemic (45).

Currently, Chinese treatment guidelines list interferon as an alternative agent for treatment. Some other immunomodulatory agents, such as baricitinib, imatinib, dasatinib and cyclosporine might work towards inhibiting SARS-CoV-2 (46).

Virus blocking and pathway inhibitors. At present, targeting the renin-angiotensin system (RAS) is an important approach for the treatment of pulmonary diseases (47-49). ACE/AngII/AT1R is an important factor in promoting acute lung injury, which can be alleviated by the antagonistic role played by ACE2/Ang (1-7)/Mas receptor pathway (45,50). Therefore, it is predicted that the combination of SARS-CoV-2 and ACE2 would inhibit the ACE2/Ang (1-7)/Mas receptor pathway (39) and decrease the ratio of ACE2/ACE, particularly in the elderly patients. However, the activity of ACE/AngII/AT1R pathway increased, thus leading to an unbalanced RAS. Then the increased inflammatory factors would increase mortality rate. Thus, activation of the ACE2/Ang (1-7)/Mas signaling pathway or inhibition of the ACE/Ang II/AT1R pathway may be an important therapeutic choice for COVID-19. In light of this fact, two ACE2 activators, resorcinolnaphthalein and 1-[(2-dimethylamino)ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl) sulfonyloxy]-9H-xanthene-9-one can be alternative therapies for COVID-19 (51). Under controlled blood pressure, the application of ACE inhibitors (ACEI) and AT1R inhibitors in COVID-19 patients may reduce pulmonary inflammation and mortality (52).

In addition, it is reported that APN01, a soluble recombinant human ACE2 (rhACE2), can block virus cell entry by competitively intercepting the SARS-CoV-2. There are some predictive drugs that can prevent the virus from invading, such as camostat, nafamostat, bromhexine, aprotinin, chlorpromazine, baricitinib, and ruxolitinib (7). However, these drugs need more clinical trials to test their efficacy and safety.

In case of cellular signaling pathway inhibitors, the potent protein kinase B (PKB, Akt) inhibitors MK-2206, niclosamide, diltiazem, nitazoxanide, tizoxanide and valinomycin, and the inhibitors of ERK/MAPK and PI3K/AKT/mTOR signaling pathways such as sirolimus, everolimus and metformin are being studied in clinical trials to verify their effectiveness (7).

Suppression of cytokine storms and bacterial infections. Zhang *et al* (53) proposed a treatment program that shortened the course of the disease in critically ill patients. The study reported that cytokine storms were found in critically ill patients. Through the artificial liver blood purification technology, inflammatory factors were removed and cytokine storms were eliminated, resulting in improved patient symptoms of breathing difficulties and blood oxygen saturation. The intestinal microecology of these patients is often disordered; therefore, a treatment method should be adopted to ensure microecological balance and to provide enteral nutrition, supplement microecological regulators, and combine with Traditional Chinese medicine (TCM) treatment to reduce secondary infection caused by bacterial transfer (54).

At the same time, a recent study stressed on the blood purification treatment for patients with severe COVID-19 (55). Immune damage mediated by cytokine storms and concomitant acute kidney injury (AKI) is a key factor for poor prognosis (55). Therefore, blood purification is urgently needed in critical cases, and its application should follow the detailed principles and protocol involved. The blood purification techniques include continuous renal replacement therapy (CRRT), blood/plasma perfusion, absorption, plasma replacement, and other modes of comprehensive blood purification (47).

In addition, there are also other ways to suppress cytokine storms, such as non-steroidal anti-inflammatory medication, immunosuppressants, IFN-λ, corticosteroids, cytokine antagonists, blockers and inhibitors, intravenous immunoglobulin (IVIg), mesenchymal stem cells, sphingosine-1-phosphate receptor 1 agonists, and enabling an increase in vascular permeability (44,56,57). IL-6 is a key factor in immune imbalance, hence it also serves as a target for drugs such as tocilizumab and sarilumab, which are currently on trial (46).

Nucleoside analogues and protease inhibitors. Nucleoside analogues that have been approved or are under development may have the potential to treat novel coronavirus infections, including favipiravir, ribavirin, remdesivir and galidesivir. They are usually derivatives of adenine or guanine. They can be used by RNA-dependent RNA polymerase (RdRp) to synthesize RNA strands; however, when integrated into the RNA strand, they block the continued synthesis of the RNA strand, leading to an early termination of its synthesis. They can be used to treat a wide spectrum of RNA viruses, including coronaviruses. Some approved protease inhibitors such as disulfiram, lopinavir, and ritonavir show inhibitory activity against SARS-CoV and MERS-CoV (58,59). These results suggest that these drugs may be used to treat COVID-19. Likewise, the inhibitors towards SARS-CoV-2 M^{pro}, such as (S)-N-Benzyl-3-(S)-2-cinnamamido-3-cyclohexylpropanamido)-2-oxo-4-((S)-2-oxopyrrolidin-3-yl) butanamide (referred to as 11r), pyridone-containing α-ketoamide derivative of 11r (referred to as 13b) and nelfinavir, can also block virus infection (7).

Anticoagulant therapy. Inflammatory factors and lymphocyte subsets are routinely monitored during the course of the disease. To enhance the immune function of patients and inhibit the formation of inflammatory factor storms, IVIg and low molecular weight heparin (LMWH) anticoagulant therapy could be given as early as possible when T cells, B cells, inflammatory cytokines, and D-Dimer show the following trends: Significantly lower T lymphocyte and B lymphocyte levels in peripheral blood than before, increase in inflammatory cytokines, abnormal increase in coagulation parameters such as D-dimer, and indication of lung lesion expansion on chest CT (59). Specifically, high-dose IVIg at 0.3-0.5 g/kg weight of the patient per day for 5 days, and 100 U/kg weight of LMWH per 12 h by subcutaneous injection for at least 3-5 days may be administered (50,60). Then, in order to avoid side effects after anticoagulant treatment, the indicators of laboratory results should be closely monitored.

It is recommended that targeted therapy be applied for COVID-19 patients with different degrees of coagulation

dysfunction. For example, when patients experience coagulation dysfunction and liver failure, the plasma exchange should be used to clear some harmful substances and supplement coagulation factors (61).

Vaccine research. Cytotoxic T lymphocyte (CTL) and B cell epitopes in the SARS-CoV-2 (50) surface glycoprotein are viable targets for vaccine research. By taking an immunoinformatics approach, Baruah and his colleagues identified five CTL epitopes, three sequential B cell epitopes and five discontinuous B cell epitopes, a result that may pave the way to develop a vaccine (62). In addition, since SARS-CoV-2 belongs to the same family as SARS-CoV and MERS-CoV, the previous experience in investigating SARS and MERS vaccines can be used to guide the development of a COVID-19 vaccine (63).

In addition, there are some other strategies based on different principles to develop vaccines. For example, RNA vaccines are produced through loading vaccines with viral messenger ribonucleic acid (mRNA), and then injected into the body. The immune cells can recognize the viral protein encoded by viral mRNA and produce antibodies. The candidate RNA vaccines include Lipid nanoparticles (LNP)-encapsulated mRNA, LNP-encapsulated mRNA encoding RBD, and LNP encapsulated mRNA cocktail encoding virus-like particles (VLP). DNA vaccines are based on recombinant DNA technology and genetic modification. This vaccine can stimulate both humoral and cellular immunity (64). And there are some DNA vaccines such as ChAdOx1 nCoV-19 and INO-4800 undergoing clinical trials (65,66). Besides, the vaccines based on protein subunits, viral vectors, VLPs, inactivated virus and live attenuated virus all have good prospects (46). These candidates may help fight infection and transmission of the virus. It should however be ensured that the condition or health status of the patient is considered before these agents are put to use.

4. Prognosis

Following systematic treatment, clinical symptoms of the patients gradually improve until they recover. However, it should be noted that there are some factors influencing the prognosis of patients with COVID-19; these can be seen in Table III.

Changes in laboratory results. By analyzing the entire course of treatment of a patient for COVID-19, it can be concluded that as the treatment progresses, the body temperature of the patient returns to normal, other clinical symptoms are significantly reduced and the levels of cytokines such as IL-2, IL-6, IL-7 and TNFα decrease gradually (67). In addition, after effective treatment, the levels of white blood cell (WBC), lymphocyte, CRP, D-dimer, ESR, and other indicators in the blood become normal. However, if these laboratory results are abnormal, the patients may have poor prognosis. As reported, cytokine storms occur in critically ill patients. Therefore, in the later stage of the disease, high levels of cytokines suggest a poor prognosis. The concomitant AKI is also a factor for poor prognosis. Usually, patients meet the criteria for discharge from isolation or hospitals when their respiratory pathogenic nucleic acid tests show two consecutive negative results (the sampling interval should be at least one day) (68). However, in the case of some infantile infections, the nucleic acids were detected in sputum and feces, even though three consecutive swabs tested negative in the same period (69). Therefore, attention should be paid to the risk of patients excreting the virus during recovery and becoming infectious. It is also significantly associated with the patients' poor prognosis. Additionally, the viral load reflected in the results of RT-PCR can also be used to predict the prognosis, for the heavy vial load may lead to poor prognosis.

T cells, especially $CD4^+$ T cells and $CD8^+$ T cells, play a significant antiviral role in the body (70). $CD4^+$ T cells promote the production of virus-specific antibodies by activating T-dependent B cells. $CD8^+$ T cells are cytotoxic and can kill virus-infected cells. In addition, it is reported that depletion of $CD8^+$ T cells does not affect and delay viral replication in SARS-CoV infection (71), but loss of $CD4^+$ T cells is accompanied by reduced production of lymphocytes neutralizing antibody and cytokine, resulting in interstitial pneumonitis and delayed clearance of SARS-CoV-2 (72). Moreover, memory T cells can defend the reappearance of viruses and the effect can last up to 11 years after the first infection (73). Thus, it can be predicted that the ratio of $CD4^+$ T cells to $CD8^+$ T cells can be used as an indicator to assess the prognosis of patients (74), and it may also be applicable to COVID-19 because SARS-CoV-2 bears a striking resemblance to SARS-CoV.

In addition, the number and the dynamic changes of platelets and platelet-to-lymphocyte ratio (PLR) were also worthy of attention in severe cases. A high PLR may indicate poor prognosis (75).

Changes in CT findings. In a SARS-CoV-2 infection, the imaging features and total CT score vary throughout the course of the disease, from initial diagnosis until patient recovery. Most patients showed the greatest severity of lung disease on CT ~10 days after initial onset of symptoms. Improvement in chest CT reports began ~14 days after the onset of initial symptoms (76). Patients with mild disease showed less inflammation and injury to lungs when compared with critically ill patients (77). According to the analysis of imaging features, pleural effusion is rare in cases of COVID-19 (78). Hence, the presence of pleural effusion and diffuse alveolar damage patterns might suggest poor prognosis, as do the high incidences of consolidation, linear opacities, crazy-paving pattern, bronchial wall thickening, lymph node enlargement and pericardial effusion (79). In summary, analysis of CT findings might be useful to predict the clinical outcome and patient prognosis. If clinicians can deduce specific patterns of lung abnormalities from CT scans, patient prognosis can be efficiently predicted. In addition, elderly individuals and those with chronic underlying diseases also have poor prognosis (6).

Serum antibodies and the titer. As mentioned earlier, the plasma from recovered patients can be used to treat critically ill patients because of the viral specific antibodies present in the plasma (53). Since the antibodies have protective effects, they can help to resist the invasion of SARS-CoV-2 again. Therefore the antibodies and their titer can also be used to predict the prognosis of the disease.

Table III. Factors influencing the prognosis of COVID-19.

Classification	Factors
Changes in laboratory results	Body temperature and other clinical symptoms, cytokine levels, the levels of WBC, lymphocyte, CRP, D-dimer, ESR and other indicators (62), acute kidney injury, the ratio of $CD4^+$ T cells to $CD8^+$ T cells (69), the number and the dynamic changes of platelets, platelet-to-lymphocyte ratio (PLR) (70).
Changes in CT findings	Pleural effusion, diffuse alveolar damage pattern, consolidation, linear opacities, crazy-paving pattern, bronchial wall thickening, lymph node enlargement, pericardial effusion (74).
Serum antibodies and titer	Specific IgG, IgM (53)
Individual factors	Cardiovascular disease, myocardial injury, diabetes or some other comorbidities (75,76), time from illness onset to antiviral treatment, age (77), level of (HFABP) (78).
Complications	Disseminated intravascular coagulation (79,80).

WBC, white blood cell; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IgG, immunoglobulin G; IgM, immunoglobulin M; HFABP, heart-fatty acid binding protein.

Individual factors. Differences in host susceptibility to viruses and immune systems can also be considered as important prognostic factors. Recently, some studies show that cardiovascular diseases such as hypertension increased the incidence and severity of coronavirus infection (80). Also, myocardial injury caused by coronavirus infection contributed to poor prognosis (81). At the same time, diabetes or some other comorbidities, and the time span between illness onset and antiviral treatment are major factors influencing the prognosis (57). Age also plays a significant role in prognosis. Patients above the age of 65 are at a higher risk of disease progression (82). Yin *et al* (83) reported that high levels of heart-fatty acid binding protein (HFABP) in blood samples of patients is closely associated with poor prognosis.

Disseminated intravascular coagulation (DIC). Disseminated intravascular coagulation frequently occurred in patients with COVID-19 with serious respiratory failure, and was considerably more frequent in non-survivors (71.4%) compared with survivors (0.6%) (12,84). These results provide evidence that DIC can be listed as a prognostic parameter of COVID-19.

It is of utmost importance to monitor the current pandemic and adopt some measures to prevent recurring outbreaks. For example, strengthening our immune system as much as possible and restricting exposure to virus, reactive/tactical treatments, vaccines, and eliminating factors that weaken immune system should be considered (85). A lot of researches have reported some factors can strengthening the immune system, such as diet with enough proteins, nutrition, exercise and adequate sleep (86). For reducing exposure to virus, the approach includes wearing masks, washing hands well, setting quarantine and reducing large gatherings (81). The factors that weaken immune system include unhealthy lifestyle, medication or radiation, occupational or environmental factors. These factors need to be eliminated as far as possible.

5. Conclusion

Presently, there are no clear treatment options for COVID-19. Much of the treatment depends on experience, along with symptomatic and supportive care. Some drugs have been chosen based on previous studies (28,46,58) on coronaviruses, including lopinavir, ritonavir, favipiravir, ribavirin, remdesivir and galidesivir. These drugs can target viruses or treat lung diseases. Notably, corticosteroids should be used with caution, as they may inhibit the immune response of the body during inhibition of lung inflammation, and are best used in severe cases. For critically ill patients, plasma therapy is a viable option. The plasma from recovered patients contains virus-specific antibodies, which can effectively prevent infection. However, some serious side effects of transfusion also need to be considered. Pregnant women should be treated with caution. Moreover, TCM has also shown promise as a COVID-19 treatment option. In general, the key to manage COVID-19 is to effectively inhibit the conversion of mild cases to severe or critical ones. Therefore, an accurate indicator to measure trends, such as oxygenation index, lymphocyte count, and cytokine levels, is required. In addition, the effective treatment of severely ill patients with the help of oxygen therapy, ventilator support, endotracheal intubation, artificial lung, anticoagulant therapy, plasma exchange and continuous blood purification should be strengthened. Research to develop drugs that prevent the virus from entering the host cells or inhibit their growth in the cells holds good promise in the battle against the SARS-CoV-2 infection. Specific vaccines can effectively suppress virus infection and intensive research on vaccine development is already underway to contain the pandemic. However, complete eradication of the disease is far from being in sight.

The health status and virus susceptibility of a patient are important factors that need to be considered to develop a prognosis of the disease. Elderly individuals, patients with cardiovascular disease and those with chronic underlying diseases have poor prognosis. In terms of imaging, the

degree of lung inflammation and injury, the presence or absence of pleural effusion and the incidences of consolidation, linear opacities, crazy-paving pattern, bronchial wall thickening, lymph node enlargement and pericardial effusion can provide clues to prognosis. SARS-CoV-2 primarily causes pulmonary diseases due to its invasiveness into the lungs. Therefore, factors such as smoking that cause lung damage, may exacerbate symptoms of COVID-19, thus leading to poor prognosis. In addition, immune system responsiveness is significantly correlated with prognosis. For example, patients with a high ratio of $CD4^+$ T cells to $CD8^+$ T cells and high titer of specific protective antibodies also have good prognosis. However, it is worth noting that an overactive immune response, such as a cytokine storm, can be damaging. Besides, aberrant laboratory indicators, such as WBC, lymphocyte, CRP, ESR and D-dimer, are also predictors of poor prognosis. Failed detection of the virus in patient samples or false-negative results could also lead to poor prognosis. As lockdown restrictions throughout the world ease, the dynamics of the pandemic still requires close observation, in order to improve its prognosis.

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Authors' contributions

XL and TL conceived and conceptualized the study. HW contributed to the acquisition of the data. XL wrote the original draft. XL, TL and HW wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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